Scabies: molecular perspectives and therapeutic implications in the face of emerging drug resistance

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Limited effective treatments, coupled with recent observations of emerging drug resistance to oral ivermectin and 5% permethrin, raise concerns regarding the future control of scabies, especially in severe cases and in endemic areas where repeated community treatment programs are in place. There is consequently an urgent need to define molecular mechanisms of drug resistance in scabies mites and to develop and assess alternative therapeutic options, such as tea tree oil, in the event of increasing treatment failure. Molecular studies on scabies mites have, until recently, been restricted; however, recent advances are providing new insights into scabies mite biology and genetic mechanisms underlying drug resistance. These may assist in overcoming many of the current difficulties in monitoring treatment efficacy and allow the development of more sensitive tools for monitoring emerging resistance.

Scabies is an infectious skin disease caused by the burrowing ectoparasitic mite *Sarcoptes scabiei*. It has remained a health problem for centuries, although its importance is frequently underestimated. The link between streptococcal pyoderma and scabies is being increasingly recognized, with high rates of acute post-streptococcal glomerulonephritis, acute rheumatic fever and rheumatic heart disease observed in Aboriginal communities in northern and central Australia [1,2]. The burden of scabies remains high in these communities despite recent mass-treatment interventions with 5% permethrin [3,4].

Limited effective treatments are available for scabies. The problem is further exacerbated by difficulties in accurate diagnosis [5] and the increasing threat of acaricide resistance. In this review, therapeutic options for scabies will be briefly outlined, the emergence of drug resistance will be discussed and recent molecular advances will be highlighted.

Treatment of scabies: present & future

It is critical that both the patient and their potential contacts are treated adequately, regardless of the acaricide used. Topical acaricides need to be applied to the entire body, including under the nails, and left on the skin for the recommended time. Additionally, because no acaricide has been confirmed to have ovicidal properties, retreatment may be necessary in some cases to kill newly hatched mites. As clinical symptoms are complicated by delayed onset of up to 6 weeks following the establishment of infection, a frequent cause of recurring scabies is reinfestation from untreated contacts. Therefore, it is essential that contacts are treated regardless of symptoms.

In developing regions of the world, cost and availability of the acaricide are of obvious importance when selecting the most appropriate treatment for scabies. Ideally, the acaricide should be easy to apply, minimally absorbed through the skin, nontoxic for the host, effective against both mites and eggs, and effective as a single-dose regimen. However, from the most widely used treatments (Table 1), no drug currently fulfils all these criteria.

Although crotamiton is currently recommended in northern Australia for treating babies less than 2 months of age [6], low efficacy has been reported in clinical trials [7,8]. This raises the issue of whether crotamiton is appropriate for controlling infant scabies in the community setting, especially considering the high burden of scabies in this group [9]. Recent studies by our laboratory, however, now confirm that 10% crotamiton has potent acaricidal properties *in vitro* (Figure 1). These results support the rationale for further exploration of crotamiton as an acaricide, possibly looking at different treatment regimes, alternative formulations to improve bioavailability or even its incorporation into combined treatment strategies.

While benzyl benzoate is highly efficacious *in vivo* and *in vitro*, treatment guidelines for this drug vary, with some recommending three applications within 24 h [10]. Given its potency and propensity to cause significant skin irritation, this regimen may be excessive. Nevertheless, since this is one of the few acaricides where resistance has not been described, its use today remains relevant.

Keywords: drug resistance, ivermectin, permethrin, scabies, treatments

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Table 1. Overview of current treatments for scabies.

Treatment	Dosage	Advantages	Disadvantages/contraindications
Sulphur	2–10% precipitate in petroleum base	Safe for infants, pregnant and lactating women; inexpensive	Noxious and malodorous, and may cause skin irritation; multiple treatments required; lack of safety and efficacy data
Crotamiton	10% ointment	Safe for infants; reported antibacterial and antipruitic activity; low toxicity; well tolerated	Clinical efficacy questionable; multiple treatments required; resistance reported
Benzyl benzoate	25% ointment	Effective; inexpensive	Can cause severe skin irritation; contraindicated in pregnant women and infants
Lindane	1% lotion or cream	Effective; inexpensive	Can cause numbness, cramps, dizziness, seizures in children; contraindicated in pregnant women and infants; resistance reported; withdrawn in several countries owing to neurotoxicity concerns
Permethrin	5% cream	Effective; well tolerated; safe	May rarely cause skin irritation; expensive; resistance reported
Ivermectin	Oral, 200 µg/kg	Broad-spectrum antiparasitic; convenient; few side effects	Contraindicated in pregnant women and infants (owing to current lack of safety data); optimal dose regimen uncertain; expensive; resistance reported

Permethrin has replaced lindane as the first-line treatment for scabies in Australia, the UK and the USA [11]. It has also been implemented for community mass treatment of scabies in Panama and Australia [3,4,12]. One of the few caveats of permethrin is that it is the most expensive topical acaricide, a consideration that restricts its use in developing regions.

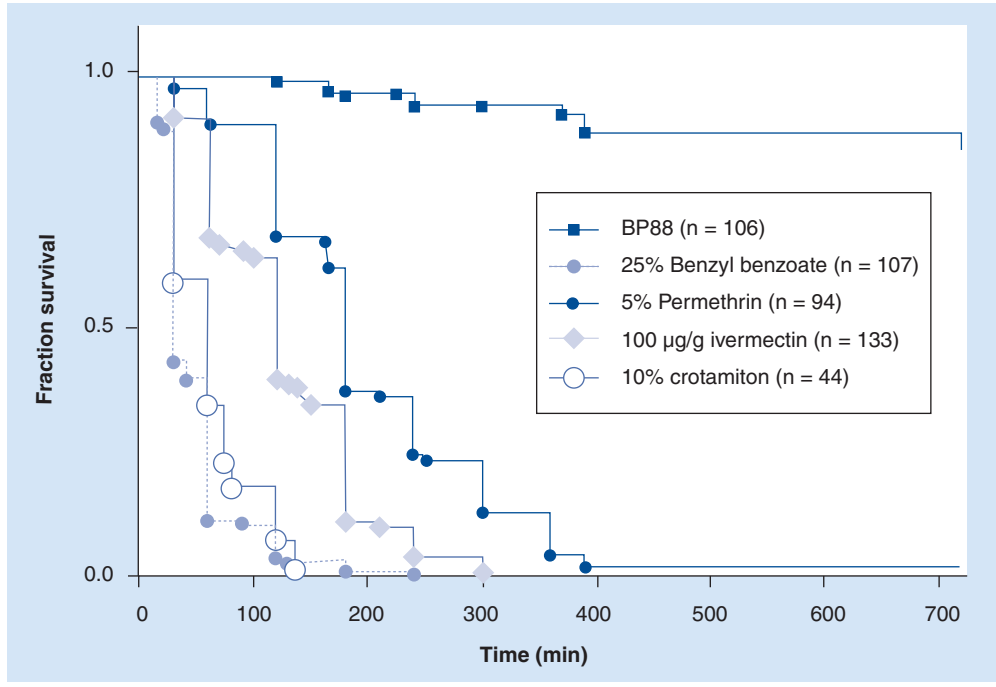
Ivermectin: a magic bullet?

The discovery of ivermectin represented a major advance in parasite control for both veterinary and human medicine. More than 400 million doses of ivermectin have been administered in programs aimed at control of onchocerciasis and other filarial diseases [13]. Ivermectin is the only acaricide that can be administered orally, making it convenient for use in institutional settings and for crusted scabies, where topical application is difficult and may not adequately penetrate the thick crusts (Figure 2). The drug has been recently approved in France, the Netherlands and Mexico for the treatment of scabies. Ivermectin has also been approved on compassionate grounds for the treatment of crusted scabies, particularly in northern Australia.

It was initially envisaged that treatment with single-dose ivermectin would replace topical creams entirely, greatly simplifying treatment of scabies [14,15]. However, this has not yet occurred for a number of reasons, including uncertainty regarding the optimal number of doses, the optimal interval between doses and drug concentration. In the few randomized-controlled trials conducted using ivermectin, there has been substantial heterogeneity in study methodology, making its clinical efficacy difficult to evaluate [16]. Recently, Lawrence *et al.* reported the success of ivermectin mass treatment of scabies in the Solomon Islands [17]. All residents received a single dose, with children under 15 kg and pregnant women treated with permethrin. Scabies prevalence rates dropped from 25% to less than 1%, and remained low for many months after the intervention. These results suggest that ivermectin may hold promise as a tool for community-based treatment of scabies, although its higher cost when compared with topical therapies may limit its applications in some regions.

Alberici *et al.* compared ivermectin and benzyl benzoate in HIV-associated crusted scabies [18]. The investigators found that neither drug was effective when used in isolation and that combination therapy was the best option. Similarly, our experience with crusted scabies patients in northern Australia strongly supports combination treatment, including

Figure 1. *In vitro* sensitivity of *Sarcoptes scabiei* var. *hominis* mites to routinely used acaricides in northern Australia.



Mites were collected from crusted scabies patients admitted to Royal Darwin Hospital (Australia) and sensitivity assays conducted as described in Walton *et al.* [29]. Data is shown for the years 2006–2007. All treatments tested show significant acaricidal activity *in vitro* when compared with the control compound (emulsifying ointment BP88). Benzyl benzoate ointment is the fastest acting acaricide *in vitro,* followed by crotamiton, ivermectin and permethrin.

multiple doses of ivermectin and topical acaricides [19–21]. Despite such comprehensive treatment regimens, failures have been reported (see later).

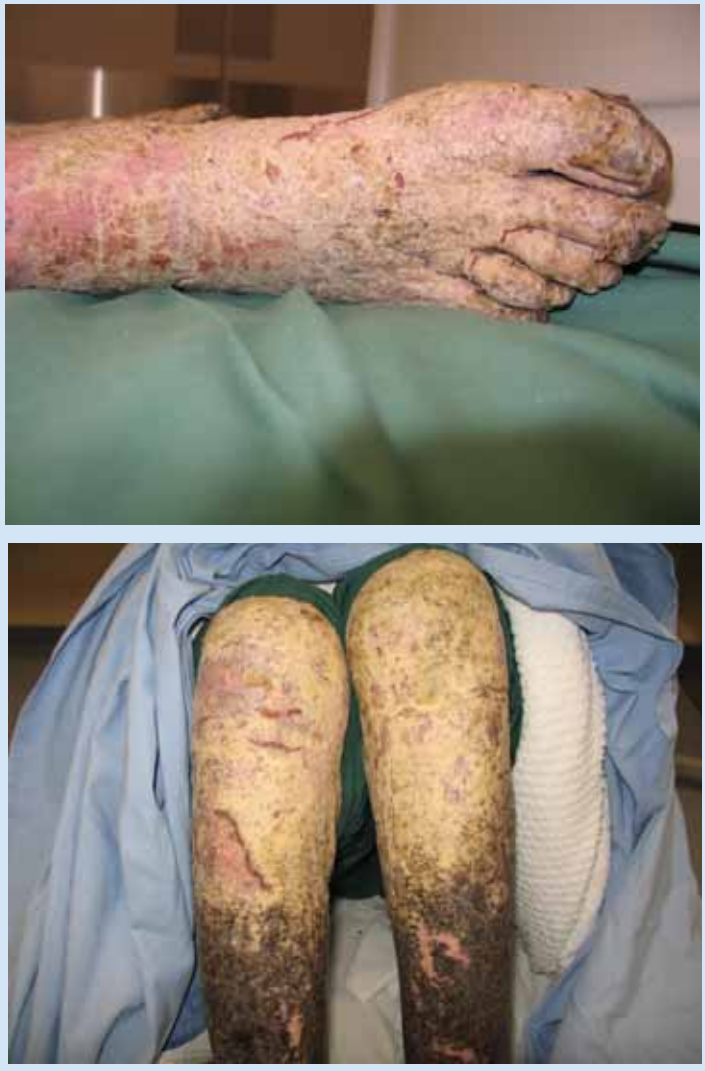
Owing to the possibility that the blood–brain barrier is incompletely developed in infants, raising the potential for ivermectin neurotoxicity, the drug is currently contraindicated in children under 15 kg and in pregnant and lactating women [22]. Despite these concerns, ivermectin has been used in these groups with no adverse effects [23], but owing to a lack of comprehensive safety data, this barrier remains. Before ivermectin can be employed as an acaricide on a widespread scale, particularly in a mass treatment strategy, its safety in young children needs to be more rigorously assessed.

Alternative therapeutic agents

Several natural agents with acaricidal properties have been described. These include lippia oil (*Lippia multiflora)* [24], camphor oil *(Eucalyptus globulus)* [25] and pastes of turmeric *(Circuma longa)* and neem *(Azadirachta indica)* [26]. Although high cure rates (97%) were obtained with the latter, neem was found to have little acaricidal properties *in vitro* [27].

One promising new treatment is tea tree oil. Derived from *Melaleuca alternifolia*, tea tree oil is a traditional Australian Aboriginal medicine used for skin infections and insect bites, and this essential oil has demonstrated antimicrobial activity [28]. However, its potential as an antiparasitic had not been explored until recently. *In vitro* studies revealed that at a concentration of 5%, tea tree oil had excellent acaricidal properties [29]. In current treatment protocols for crusted scabies at Royal Darwin Hospital (Australia), benzyl benzoate ointment is supplemented with 5% tea tree oil [30]. Not only is this a potent combination *in vitro* [29], but the addition of tea tree oil helps to reduce the significant irritation experienced with benzyl benzoate [Unpublished Data]. However, more data regarding the safety and *in vivo* efficacy of topical tea tree oil through clinical trials are required before its widespread promotion as a therapeutic agent for scabies can occur.

Figure 2. Crusted scabies.



This extreme manifestation of scabies is characterized by a proliferation of mites and formation of hyperkeratotic skin crusts. Recurrent episodes of crusted scabies can result in considerable skin depigmentation. Fissuring of skin crusts, particularly around joints, can be a source of serious secondary bacterial infection.

Acaricide resistance: clinical & *in vitro* observations

Traditionally, treatment failures for scabies are attributed to incorrect application of the acaricide, or failure to treat contacts leading to reinfestation. However, there are now reports of treatment failures linked with drug resistance. Of particular concern is the potential emergence of resistance to the two major acaricides – permethrin and ivermectin. In addition, resistance to other acaricides, such as lindane and crotamiton, have also been reported worldwide [31–33].

Permethrin resistance

Permethrin resistance in other ectoparasites, such as head lice, is widespread (reviewed in [34]). This suggests that its emergence in scabies mites is a real possibility. In humans, while clinical resistance of scabies mites to permethrin is yet to be documented, anecdotal reports of failure in Australian remote communities receiving mass treatment are growing [Unpublished Data]. Furthermore, longitudinal studies conducted in northern Australia confirm increasing *in vitro* tolerance. In 1994, before widespread permethrin treatment was introduced, all mites were killed within 30 min of *in vitro* exposure to permethrin [35]. By the year 2000, however, 35% of mites were alive after 3 h of exposure and a significant proportion remained alive overnight [27]. More recent analysis confirms increasing tolerance and shows that permethrin is now the slowest acting acaricide *in vitro* in this region (Figure 1).

Ivermectin resistance

After nearly 30 years of intensive use, ivermectin resistance is now widespread in veterinary practice, and may now be emerging in filarial nematodes affecting humans [36]. There is now data suggesting that on a genetic level, ivermectin is imposing selection pressure on several *Onchocerca volvulus* genes [37].

Ivermectin has been used for over 10 years for the management of crusted scabies in northern Australia. One patient with recurrent crusted scabies has received approximately 150 doses of ivermectin over a 13-year period, arguably the highest in the world. Since its introduction, treatment failures have been observed with ivermectin therapy for crusted scabies, despite intensive multiple-dose regimens (Box 1). Clinical and *in vitro* ivermectin resistance has now been documented in two crusted scabies patients [21]. Significantly, these were the first reports of ivermectin resistance in scabies. Furthermore, analysis of 10 years of *in vitro* sensitivity data shows that median survival times to ivermectin have doubled since its introduction [38].

Although these latter clinical cases currently appear to be isolated events, they do highlight the future uncertainty regarding the long-term usefulness of ivermectin for the treatment of scabies, especially in severe cases and in endemic regions where community-based treatment may be desired. An important consideration is that crusted scabies patients are often identified as core transmitters of scabies to others in the community, and therefore the spread

Box 1. Timeline of emerging ivermectin resistance in northern Australia.

April 1992

Ivermectin introduced for crusted scabies in northern Australia. Two doses have a negligible effect on mite burden [66]

1994

A single 240 µg/kg dose of ivermectin and multiple permethrin applications fail to resolve infestation with live mites still observed after 2 weeks [19]

1996

Three-dose regimen introduced

1997

Relapses reported to three-dose regimen, with live mites observed 19 days after third dose [20]
Genotyping studies indicate treatment failure is attributed to recrudescence, not external reinfection [44]

1998

Five-dose regimen introduced

1999

Relapses to five-dose regimen. Monthly ivermectin prophylaxis was unsuccessful at preventing reinfestation [Currie, Unpublished Data]

2000

Clinical failure of ivermectin in two recurrent crusted scabies patients, with live mites observed after a month of multiple ivermectin treatments. *In vitro* testing confirms mites have significantly increased tolerance to ivermectin, with some mites surviving overnight ivermectin exposure [21]

2004

Evidence of increased *in vitro* tolerance to ivermectin in a third recurrent crusted scabies patient, although patient responds well clinically to combination therapy with benzyl benzoate and ivermectin

2006

Little reduction in mite numbers when three doses of ivermectin administered within 1 week
Longitudinal analysis of *in vitro* sensitivity data confirms that mite survival times to ivermectin exposure have more than doubled in the 10-year period investigated [38]

of ivermectin resistant mites may jeopardize the success of future mass treatment strategies involving ivermectin.

Consequences of acaricide resistance & the need for molecular diagnosis

The emergence of acaricide resistance is a serious threat to the control of scabies. As outlined previously, there are very few effective drugs currently available for scabies, and the development of new drugs is unlikely in the near future. Scabies is a neglected disease, and although there may be potential for immunological control, a vaccine or other immunotherapy may be decades away. It is therefore essential to prolong the life of the limited available drugs if we are to achieve sustainable control of this disease.

Assessment of drug efficacy in scabies is currently based on clinical reports and/or *in vitro* drug-sensitivity studies. These can be costly, labor intensive and time consuming. Furthermore, because most scabies patients generally have fewer than ten mites present in the skin, *in vitro* studies are only possible for cases of crusted scabies and therefore their application is limited. The development of molecular methods for assessing drug susceptibility would enable much greater sensitivity, and genetic changes associated with resistance could be detected before they are widely prevalent. While molecular tools have been developed and applied to monitor parasitic drug resistance in many medical, veterinary and agricultural settings (for examples see [39–41]), little work has been undertaken in human scabies.

Molecular mechanisms for permethrin & ivermectin resistance

Factors influencing the emergence of drug resistance [42] include the biology and life cycle of the parasite [43], and the genetic diversity of the parasite prior to drug selection. Increased diversity also increases the likelihood of resistance alleles existing in a population before selection. How

does this apply to the emergence of resistance in scabies? Scabies mites have a short, direct life cycle that may favor resistance development. In ordinary scabies, reproductive success and resulting mite populations are kept relatively low owing to host immunity, but the opposite is true for crusted scabies. Indeed, microsatellite studies confirm substantial genetic heterogeneity, with up to 46 alleles at a particular locus reported in a single population of mites obtained from a crusted scabies patient [44].

Mechanisms for resistance to topical pesticides in arthropods are well established and include:

- Target alteration, for example, mutations to the voltage-sensitive sodium channel, the target of pyrethroid insecticides;
- Increased enzymatic degradation by esterases (e.g., carboxylesterase B1), or other detoxification enzymes, such as the cytochrome P450 and glutathione *S*-transferases [45–48].

Molecular evidence suggests that ivermectin-resistance mechanisms are complex, multifactorial and may differ between closely related organisms [42]. However, several candidate mechanisms are well established. Changes to the target of macrocyclic lactones, the ligand-gated chloride channels, have been implicated in ivermectin resistance in several nematode and arthropod species [49–51]. Ivermectin is an excellent substrate for ATP-binding cassette (ABC) transporters, such as P-glycoprotein, which are associated with multidrug resistance through efflux pumps in many species. Allelic selection at P-glycoprotein has been associated with ivermectin exposure in several nematode species, including *O. volvulus* [52,53]. Increased transcription of P-glycoprotein among ivermectin resistant nematodes has also been reported [54]. Several non-P-glycoprotein ABC transporter genes from *O. volvulus* also show selection after ivermectin treatment [55]. Additionally, studies in arthropods of resistance to the related macrocyclic lactone abamectin advocate a role for metabolic mechanisms [56,57], although limited molecular data are available to support this.

Scabies mite gene discovery

Until recent years, there had been little progress in understanding the molecular biology of *S. scabiei*, primarily because of limitations in obtaining sufficient genetic material. Owing to their access to *S. scabiei* mites from crusted scabies patients, our group has overcome this problem, and initiated the first ever DNA-based studies on scabies in the mid-1990s [58]. We are now making rapid progress in our understanding of molecular mechanisms of both permethrin and ivermectin resistance in scabies mites. The partial genomic and cDNA sequence of the scabies mite voltage-sensitive sodium channel has been identified, facilitating single nucleotide polymorphism identification in permethrin-resistant mites [59]. Studies on permethrin resistant *S. scabiei* var. *canis* have identified a *kdr* type mutation not present in mites unexposed to permethrin, but this has not been identified in any var. *hominis* populations to date [60]. Two *S. scabiei* glutathione *S*-transferases have been identified and sequenced [61,62]. Eight ABC transporter genes have been recently identified from *S. scabiei*, five of which belong to subfamilies implicated in drug resistance in other organisms [63]. Subsequently, a quantitative PCR assay has been developed to study transcription of these genes and observed increased mRNA levels of an ABC transporter gene in ivermectin-exposed mites [Mounsey, Manuscript in prepraration]. Additionally, a novel ligand-gated chloride channel has been identified and characterized in the *Xenopus laevis* expression system. Significantly, this channel was irreversibly activated by ivermectin, suggesting it may act as a drug target *in vivo* [64].

Conclusions

Although scabies is an ancient disease, treatment options remain limited. Over recent years permethrin has emerged as the topical agent of choice owing to its efficacy and high tolerability, although there are concerns regarding emerging tolerance. Despite its promise, there are still several unresolved issues regarding the use of oral ivermectin for both ordinary and crusted scabies.

Importantly, the uncertainty regarding therapeutic ivermectin and permethrin concentrations *in situ* should also be examined if we are to fully understand their pharmacodynamics. In humans with ordinary scabies, levels of ivermectin in skin reached peak concentration within 8 h and declined markedly after 24 h [65], suggesting selective pressure would remain low. The opposite may be true in crusted scabies, where sub-therapeutic drug concentrations in hyperkeratotic skin crusts may occur for prolonged periods, favoring selection for drug-resistant mites, particularly under a multiple-dose regimen.

Improved surveillance for emerging resistance to acaricides is critical. In addition, defining the genetic basis of resistance will facilitate the development of molecular approaches to enable

more effective monitoring and control for the spread of resistance in scabies endemic communities. In the meantime, continued *in vitro* testing remains an important adjunct to routine clinical practice for individual patients and during community mass treatment initiatives to ensure the ongoing successful treatment of scabies.

Future perspective

In light of emerging drug resistance, the use of alternative agents should be considered. For example, benzyl benzoate and crotamiton are both very effective acaricides *in vitro* and could be revisited in the clinical setting. However, this is hampered by the fact that few robust clinical trials exist for scabies treatments, and this needs to be addressed as a matter of priority. Tea tree oil is a promising new topical therapy, particularly when used in combination with other treatments. Not only may this be associated with improved treatment outcomes, but combination therapies could become increasingly useful and important in the event of increasing drug resistance.

One of the current difficulties in assessing drug resistance is limited access to mites with a clear resistance phenotype. Studies are currently restricted to mites obtained from the clinical setting, and therefore there are inevitable confounders, such as physiological factors and co-administration of other drugs, making definition of true resistance difficult. Fortunately, the further development of an animal model for human scabies is currently being attempted and may become available in the near future. The generation of laboratory selected drug-resistant strains will open up a new realm of possibilities, allowing the consolidation of recent molecular progress with phenotypic changes potentially associated with developing resistance.

Executive summary

The problem with scabies

- Scabies remains a significant health problem, especially in developing and disadvantaged populations. The apparent link between scabies and complications of streptococcal pyoderma has led to concerted efforts to reduce rates of scabies in northern Australian Aboriginal communities.

Therapeutic options

- Difficulties with diagnosis and a lack of quality clinical trials make it difficult to evaluate optimal therapeutic strategies for scabies. The first-line treatment in many countries is now 5% permethrin, with ivermectin, a promising oral therapy for ordinary scabies. Benzyl benzoate continues to be highly efficacious, although there are problems with its tolerability. Tea tree oil looks promising as a new topical therapy.

Threats of resistance

- Clinical and *in vitro* resistance to ivermectin has now been documented and there are concerns regarding the increasing tolerance of scabies mites to permethrin.
- There is an urgent need to define molecular mechanisms of drug resistance in order to detect its emergence more rapidly, providing more options to control its spread.

Recent molecular advances

- New molecular studies are shedding light on potential drug resistance mechanisms in scabies mites. Several key molecules have been characterized, including the permethrin-sensitive sodium channel gene, an ivermectin sensitive ligand-gated chloride channel, and several ABC transporter genes and glutathione *S*-transferases.

Future perspective

- A rigorous evaluation of all currently available acaricides via clinical trials may provide acceptable alternative therapeutic options in the face of emerging drug resistance.
- More needs to be understood regarding ivermectin pharmacokinetics in relation to optimal treatment for both ordinary and crusted scabies. Safety issues regarding the use of ivermectin in children less than 15 kg and in pregnancy should be addressed in clinical studies.
- Continued molecular advances, coupled with laboratory drug selection studies in animal models, will greatly enhance our understanding of acaricide resistance in scabies mites and will provide more sensitive tools for diagnosis and control of resistance.

The deleterious impact of scabies in developing regions worldwide is without question. We are now rapidly making advances in our understanding of the genetics of *S. scabiei*, with the characterization of key genes potentially associated with permethrin and ivermectin resistance. This will enable the development of molecular techniques to facilitate the continued monitoring, and enable the identification of emerging permethrin and ivermectin resistance in scabies endemic communities. This is important in light of increasing pressure from health professionals to begin mass intervention programs with ivermectin in endemic areas.

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